Recall Recommendation Review 30007825

To: **DOE A**

CTR 02/29/2008

Re: Recall Enterprise System (RES) Event Number: ***46685***
http://marcsrecalls.ora.fda.gov/res/jsp/General/Li_LoginCtrl.jsp

Subj: **Please classify the above Recommendation using one of the three modes below:**

Panel & Product code: _80/LKK_____ (ex. 74/MAF)
Verify Marketing Status: 510(k) _____ (PMA) P860004 Pre-amendment/Exempt (Circle One)
Consider Warning Letter if firm has no 510(k)/PMA, and this is not a pre-amendment or exempt device
What CFR and/or THE ACT violation does this Recommendation support ? Misbranding - 502(j) of FD&C Act
(21CFR_____, USC_____, Misbranding etc.)

1. [ ] Precedent recall with comparable health risk:

Z #_____. MD concurrence _____

Was a Precedent or Policy selected by the district? [ ] Yes [x] No
If Yes, is the district selected Precedent recall appropriate? [ ] Yes [ ] No
If No, search **RES** for a **Precedent Recall** with the same ***Risk to Health.***
Precedent recalls can be found on the Search page of RES, below the blue line. Or search top section for similar recall and verify HHE was used.

2. [ ] CDRH recall policy that applies: _____

1. Latex surgical glove fails leak test
2. Latex exam glove fails leak test
3. Latex condom fails leak test
4. Marketed without a 510(k) or PMA
5. Intended use not in 510(k) or PMA
6. Sterility (package integrity) compromised
7. Labeled latex free, contains latex
8. Needle stick risk
9. Fails to comply with performance standard

These recalls can be directly classified as Class II after verifying that no deaths or serious injuries are associated with the problem.

3. [x] A completed Health Hazard Evaluation (attached), w/ Medical Officer's signatur

Also e-mail completed electronic HHE form to CDRH Recall Group, with RES # in subject
OC/OIVD MD concurrence _____

The Recall Class is: (I) II III, Safety Alert, Market Withdrawal, Stock Recovery, Non-Concur
(Circle one) (if Class I, a new HHE is required)

If Recall, assign: Depth R (W=Wholesale, R=Retail/Hospital/Physician/Lab, U=Consumer/patient)
Effectiveness Level A Audit Level B (A=100%, B>10%, C=10%, D=2%, E=0)
Risk Guide- Class I: A/B or 100-300 consignee visits, -User level Class II: C/D or 2-80 consignee visits, -Retail level Class III: D/E -Wholesale level (audit/effectiveness levels)

[ ] Compare RES to Firm's Recall Letter for accuracy ! ! (Product Names, Lot Numbers, Reason for Recall etc
Classified w/o letter [ ] Center Comments* [ ] Classified w/o CAPA [ ]
Revise Recall Letter [ ] Request CAPA for review before termination [ ]
Revise Firm's Press statement [x] Revise RES* [ ] No changes needed [ ]

* (If comments, corrections or changes are needed, please check box above and send e-mail to CDRH Recall Group with RES # in subject.)

Printed name Kenneth C. Millen Signature: 3/21/08
Branch: GHDB_____ Date: February 29, 2008
Supervisor approval: Patrick Wiesty Date: 3/21/08

This form MUST BE RETURNED TO HFZ-305 Recall Team for processing

Z# 1142 | 1154-2008 [√] RES by CTR [√] e-mail to CSO by CTR [√] to Internet [ ] Oracle by _____
OCTR 125.051 02/21/2006 {QA by } [ ] Root Cause Code [√] Scanned by _____ {QA by }

APPROVED MAR 26 2008 ENTERED

Please submit comments, concerns or suggestions to oewebrequest@fda.hhs.gov

Please save as a different filename before filling out this form.
HHE Version 3-1 01/12/2007

Health Hazard Evaluation [☒]
or Health Risk Assessment [☐]
Center for Devices and Radiological Health

Date:	February 29, 2008	RES #:	46685	Safety Officer:	Kenneth C. Millen

I. Product Data

Panel Code:	80	**Device Name:**	SynchroMed EL, SynchroMed II and IsoMed implantable infusion pump systems
Product Code:	LKK		
Models:	**SynchroMed EL Models** 8626-10, 8626L-10, 8626-18, 8626L-18, 8627-10, 8627L-10, 8627-18, 8627L-18; **SynchroMed II Models** 8637-20, 8637-40; and **IsoMed Models** 8472-20, 8472-35, 8472-60	**Lot/Serial Numbers:**	All

TAB C

Marketing Status (Include 510(K) Or PMA Number, Specify If Class I Exempt From 510(K) :
PMA P860004

Total Number Of Devices In Distribution: ~102,792 pumps

U.S.: 90,330 pumps **Foreign:** 12,462 pumps

Number Of Devices Subject To Recall or Review: 102,792 pumps

U.S.: 90,330 pumps **Foreign:** 12,462 pumps

Manufacturer / Recalling Firm, Address:
Medtronic Neuromodulation
800 53rd Ave NE
Minneapolis, Minnesota 55421

Product Description (Include Intended Use From Labeling):
The SynchroMed EL/II and IsoMed pumps are implantable, programmable, battery-powered devices that store and deliver medication according to instructions received from a programmer.

SynchroMed EL Indications:
Chronic intraspinal (intrathecal or epidural) infusion of preservative-free morphine sulfate for treatment of chronic, intractable pain. Chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain. Chronic intrathecal infusion of Lioresal® Intrathecal (baclofen injection) for severe spasticity. Chronic intravascular infusion of floxuridine (FUDR), or methotrexate for the treatment of primary or metastatic cancer.

SynchroMed II Indications:
US: Chronic intraspinal (epidural and intrathecal) infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal® Intrathecal (baclofen injection) for the management of severe spasticity; chronic intravascular infusion of floxuridine (FUDR) or methotrexate for the treatment of primary or metastatic cancer. Outside of US: Chronic infusion of drugs or fluids tested as compatible and listed in the product labeling.

IsoMed Indications: To deliver the chemotherapy agent floxuridine (FUDR) for use in hepatic arterial infusion (HAI) therapy, a treatment for patients with colorectal liver cancer, and to deliver morphine to the spinal fluid as a treatment for patients with chronic intractable pain.
ORACLE #
Class: I Recall #(s) Z-1142/1154-2008

Health Hazard Evaluation or Health Risk Assessment
Center for Devices and Radiological Health

Date: February 29, 2008 | RES #: 46685

II. Problem Definition and Analysis

Reason for Recall or Risk Assessment

- **Description of the Defect, Malfunction or Error in Use of the Device:**
  Inflammatory Mass Lesions (primarily intrathecal granulomas) presenting as a chronic inflammatory or granulomatous mass lesion at the tip of the intrathecal drug delivery catheters. Unrecognized and/or untreated inflammatory mass lesions may result in serious neurological deficits (e.g., complete or partial spinal cord injury). There have been anecdotal reports of a drug precipitate forming with the use of compounded Baclofen (at high concentrations) which resembles the granulomatous mass with Magnetic Resonance Imaging.

- **Root Cause of the Problem (If Known):**
  Mass formation at or near the distal tip of the intrathecal catheter has been reported with the intrathecal infusion of opioids, baclofen, pharmacy-compounded baclofen and other drugs, as well as with other pharmacological admixtures.

- **Factors That May Contribute to Product Risk (i.e. Device Design, Manufacturing Problems or User Error):**
  Device design, device interaction with drug therapy

- **Design Factors That Might Mitigate Risk?**
  The number and orientation of holes in the catheter and the material used in construction might influence the formation of masses within the intrathecal space. The concentration, dosage, rate of drug infusion and placement of catheter may also influence the formation of masses within the intrathecal space.

- **If Device Failure Occurs Is It Easily Recognized by User?**

  The presence of a developing mass may not be known to patient or physician until symptoms appear and diagnostic imaging is performed. Inspection of the device does not indicate whether a mass will develop with use.

  Typically, prodromal symptoms and signs that could indicate presence of a mass in the intrathecal space, include:

  - Change in the character, quality or intensity of pain
  - New radicular pain, especially at or near the dermatomal level of the catheter tip
  - Frequent or large escalations of the daily drug dose are required to maintain the analgesic effect
  - Dose escalations may alleviate the patient's increasing pain only temporarily.
  - Early symptoms of mass in the thoracic spinal canal may also include thoracic radicular pain
  - Symptoms in the lumbar region sometimes simulate root compression from a herniated disc or spinal stenosis

Additionally, if the patient has pain that corresponds to the level of the catheter tip during Catheter Access Port (CAP) injections or programmed boluses, this may indicate presence of a mass.

Manufacturer's CAPA Investigation (If Available):

- **Summary:**

Taken from firm's investigation report NDHF1119-95024 and associated recommended corrective action:

The firm believes that masses could occur with any serial number for any of the device models listed above however the rate of occurrence may be related to the specific therapy, concentration and rate being infused.

This can present itself as a chronic inflammatory or granulomatous mass lesion at the distal end (delivery hole area) of intrathecal drug delivery catheters. Unrecognized and/or untreated inflammatory mass lesions may result in serious neurological deficits (e.g., complete or partial spinal cord injury).

Affects all models of SynchroMed EL, SynchroMed II and IsoMed, intrathecal catheters, and refill kits.

The firm also states in their Investigative Report that their assessment shows "....intrathecal inflammatory mass is a drug-induced phenomenon. It is not a product/device failure." (page 27 of 149, NDFH1119-95024) however findings from the MIN-DO 11/21/2006-1/24/2007 inspection noted the following regarding root cause:

- The firm has used different catheter designs - e.g., 6 side holes (8709, 8709AA, 8711, 8731, & 8598) versus the open tip (8703, 8703W) thinking that hole size or orientation might have an impact. A FMEA was performed by Medtronic in September 2003 (Model 8731 Design FMEA, 8731-70145, Version 2.0), regarding the IM/G/F growth issues in their intrathecal catheters. In that FMEA analysis, the firm cites "Contributes to inflammatory mass" as an effect of the Cause of Failure, "Holes are not ideal size or have incorrect orientation". The "Failure Mode" is, "Fluid flow out of catheter causes bodily reaction". (As of the date of the inspection, the firm has not definitively determined whether hole size or numbers have an impact.)

- In a discussion with Dr. Jeffrey W. Allen – Senior Scientist, Emerging Therapies Research, who supports the Medtronic engineering groups and helps to develop in-vivo testing and animal models, Dr. Allen mentioned a new catheter that is in development that has a permeable membrane along its length to provide better mixing in the CSF. Dr. Allen said that catheter design may help, and that current catheters are not designed to be anti-mass-forming (Page 13 of 33, FDA EIR from Inspection 11/21/2006-1/24/2007). However, a preliminary study finalized in November, 2007 by the firm has concluded that the current permeable membrane catheter (PMC), as designed, did not prevent or reduce the incidence of morphine-induced intrathecal mass formation in the hound model (Page 289, Medtronic Neuromodulation Investigation Report NDFH1119-95024).

These findings indicate catheter design may play a role in the formation of intrathecal inflammatory mass formation after infusion of opioids, baclofen, pharmacy-compounded baclofen and other drugs, as well as with other pharmacological admixtures, the risk of inflammatory mass formation appears to increase in the first 3-4 years after implant.

A medical consultant to the firm has said based on his experience that granulomatous mass lesions do not occur with use of the brand of baclofen recommended in product labeling. They may occur with the use of generic or compounded versions of the drug but are not frequent. He also indicated that a participate from generic versions of the drug may occur around the catheter tip creating an image on MRI that is similar to a granulomatous mass. The firm indicated that they have received some MDR reports for granulomatous masses with baclofen use and lack sufficient information to support or disprove this expert's view.

The firm initially said it does not believe that granulomatous masses are a device issue, rather they believed them to be a drug therapy issue. However, a voluntary recall has been initiated.

Corrective Action:
Update labeling appropriately to include risk information.
Customer communication - Physician Letter sent January 28, 2008 reminding of IM, and details on recognition, treatment and mitigation.

Preventive Action:
Continue to monitor the rate of inflammatory mass at a minimum on an annual basis.

- **Date of Analysis:**
  August 13, 2007

- **Firm's Estimate of Number of Devices that will Develop the Defect and/or Fail :**

  - **How Many Devices from the Affected Lots Are Expected to Have or Develop the Defect?**
    All intrathecal catheters could potentially be affected by the IM/G/F problem.

  - **How Many Devices with the Defect are Likely to Exhibit the Failure Over the Lifetime of the Device?**
    All intrathecal catheters could potentially be affected by the mass problem.

  - **Of Those Devices that Fail, How Many are Likely to Cause Injury if Used?**
    There is a potential for further complications, if the IM/G/F is not promptly diagnosed and treated.

  - **Any Comments on How these Estimates were Reached:**

- **Firm's Conclusion About Health Risk. (Attach a Copy of Firm's HHEs or HHAs):** See attached firm HHE

- **Any FDA Comments:**

Adverse Events, Complaints and Problems or Incidents that may be Related to the Device Defect:

Number of Complaints	603 as of February 6, 2008 MAUDE search	**Malfunction Reports**	At least 18*
Injuries Reported	**U.S.** 396*	**International**	
Deaths Reported	**U.S.** 14*	**International**	

Sources:

Manufacturer _____ **Inspection** _____ **MDR's** _____

Explanation:
*Analysis of MDR's after May 7, 2007 is not complete so the malfunction, injury and death numbers could be higher.

Describe the Complaints and Injuries Reported to Date:
Inspectional Findings:
The following list shows typical PCR's that were reported in the firm's complaint system:

PCR Number	Description
PCR 60377	Discovered granuloma via MRI. Patient experienced subarachmoid hemorrhage and paralysis.
PCR 183288	Patient reports granuloma diagnosed... following paralysis of left leg. Surgery to remove distal end of catheter with granuloma. Post op: Patient reports still paralyzed.
PCR 191620	Patient reported "fell over backwards", burning/numbing pain in abdominal, back, legs and feet. MRI found granuloma.
PCR 278679	Rep reports: Granuloma at catheter tip. Doctor states that this is the largest or 2nd largest he has ever seen.
PCR 95901	Confirmed intraspinal mass. Patient reports "pain at catheter site for three months, numbness/tingling in hands and feet, had two MRI's showing suspected granuloma."
PCR 171432	Patient reports six months of excellent symptom relief following implant in 2000, however symptoms began to return including increased pain... Granuloma in September 2003 and surgery was performed."

Health Hazard Evaluation or Health Risk Assessment
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III. Health Risks
TO BE COMPLETED BY MEDICAL OFFICER OR COMMITTEE

THE FOLLOWING ASSESSMENT IS BASED ON CURRENTLY AVAILABLE INFORMATION. CONCLUSIONS MAY CHANGE IF ADDITIONAL INFORMATION BECOMES AVAILABLE IN THE FUTURE.

Immediate and Long Range Health Consequences:

A. **Describe the Immediate and Long Range Health Consequences (Injuries or Illnesses) That May Result from Use of or Exposure to the Defective Device. (Include Known Off Label Uses)** If an inflammatory mass, fibrosis or granuloma develops, it could initially be asymptomatic. Over time, the mass can enlarge to compress the subarachnoid space and/or spinal cord, thus impinging on the exiting nerves. This could lead to temporary or permanent sensory deficit and progress to motor deficit and potential paralysis. As the mass grows in size, the flow of medication can be interrupted, thus the patient may not receive all or a portion of the desired therapy, medication could also be delivered outside of the intended area (e.g., intrathecal space). If patient experiences symptoms consistent with underdose of medication the patient may receive therapy via alternative routes or from an increased pump dosage, this may result in over-dosing of medication. Overdose of therapies such as morphine could result in respiratory depression and possibly respiratory arrest; an underdose may result in inadequate therapy. Underdose of therapies such as baclofen could result in baclofen withdrawal syndrome which can encompass neuroleptic malignant syndrome, which may result in cardiac arrhythmia and/or rhabdomyolysis, all of which could potentially lead to death. If the mass is large enough, it could obstruct the flow of cerebral spinal fluid (CSF) thus resulting in increased intracranial pressure (ICP). Inflammatory mass, granuloma, and fibrosis can itself be a seed for sepsis. These complications may require medical or surgical intervention (with the associated risks).

   There have been anecdotal reports of a drug precipitate mass forming in the intrathecal space with the use of pharmacy-compounded, high concentration Baclofen. This may have initial symptoms which are similar to inflammatory mass symptoms, however it is unknown if the long-term symptoms will differ. Diagnostic images of a precipitous mass may be difficult to distinguish from a granulomatous mass.

B. **Describe Any Clinical Factors That May Mitigate the Risk:** Follow-up MRI, other diagnostic procedures, and/or neurological assessments that lead to early identification of a granuloma. Changing therapy, adjusting the concentration of the medication, dose, and/or flow rates might mitigate the formation of the granuloma. Monitoring of dosage administration to assure that the calculated residual matches the measured residual of drug therapy.

C. **What Segment of the Population is Most at Risk? (e.g. Infants, Elderly, Pregnant Women, Critically Ill Patients, Immunocompromised, etc.)** Higher risk of granuloma formation may occur in patients receiving a high concentration of opioid therapy. After the formation of the granuloma, immuno-compromised patients, and the elderly population may be at higher risk of infections secondary to the granuloma.

D. **Does the Health Consequence Have Significant Public Health Impact Beyond Users (e.g. Spread of Serious Infection to Others)?** No

Assess the hazards associated with use of the defective product

Check All that Might Occur:

Population at Greatest Risk	Overall Population Using Device	
☒	☒	Life-threatening (death has or could occur)
☒	☒	Results in permanent impairment of body function or permanent damage to a body structure.
☒	☒	Necessitates medical or surgical intervention.
☒	☒	Temporary or reversible (without medical intervention).
☒	☒	Limited (transient, minor impairment or complaints).
☒	☒	No adverse health consequences.
☐	☐	Hazard cannot be assessed with the data currently available.

Explanation:

Assess the Probability that Use of, or Exposure to, Product under Recall will Cause Adverse Health Consequences

	Serious Adverse Health Consequences (Death, Life Threatening, Results in Permanent Impairment)		Medically Reversible or Transient Adverse Health Consequences	
	Overall Population Using Device	Population at Greatest Risk	Overall Population Using Device	Population at Greatest Risk
Every Time	☐	☐	☐	☐
Reasonable Probability that Use will Cause	☒	☒	☒	☒
Remote Probability that Use will Cause	☐	☐	☐	☐
Not Likely that Use will Cause Any Adverse Events	☐	☐	☐	☐

Explanation / Comments: The reported incidence of patients who have developed inflammatory mass (0.49%) is approximately five times higher than was reported in 2001 (0.1%). The firm states that no dose and/or concentration of morphine sulfate can be considered completely free of risk of inflammatory mass. By the firm's admission there is known under-reporting. The rate of occurrence is expected to increase with use over time.

The committee concluded that there is a reasonable probability of mass formation and related risk even for patients who have not received the higher drug concentrations.

SIGNATURE PAGE – ATTACHED BELOW

**Contributed to HHE via teleconference and concurred with risk but were not available for signatures.

Signatures	Date	Printed Name
	3/3/08	Murray Malin, M.D.**
Kimber C Richter	2-29-08	Kimber C. Richter, M.D.
		Lana Shiu, M.D. **
George Kroehling	2/29/08	George Kroehling
		Claudia Gaffey, M.D.**
		Audrey Morrison**
Daniel B. Lyle	2/29/08	Daniel B. Lyle
Valerie A. Flournoy	2/29/08	Valerie A. Flournoy
	2/29/08	Nikhil Thakur
	2/25/08	Kenneth C. Millen
Joy Arnuits - Clinical	3/1/2008	Joy Arnuits - Clinical

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2/29/08 KCM